#12 B. Webb 2/6/04

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In Re the Application of:	Group Art Unit: 1642
HOWELL et al.	Examiner: Helms, L.
Serial No.: 09/444,144	
Filed: November 20, 1999	DECLARATION OF MARK D. HOWELL AND CHERYL L. SELINSKY (37 CFR § 1.132)
Attorney File No.: 4369-1 (formerly Cyto001)	
For: METHOD FOR ENHANCING IMMUNE RESPONSES IN MAMMALS	

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on February 20, 2001.

SHERIDAN ROSS P.C.

Kathleen Bussell

KATHLEEN BUSSELL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Mark D. Howell and Cheryl L. Selinsky, each declare as follows:

1. I am a co-inventor of the above-referenced patent application and am familiar with the application.

2. This Declaration is being submitted in conjunction with an Amendment and Response After Final Rejection to an Office Action having a mailing date of December 20, 2000.

3. The following discussion is provided in traverse of the Examiner's rejection of Claims 1-3, 5, 10-27, 34, 37-38, 40-42, and 50-56 under 35 U.S.C. § 103. These comments have been discussed with the Examiner in the telephone interview of February 6, 2001, and this Declaration is provided at the Examiner's suggestion.

<u>Discussion of Lentz</u>

The Examiner contends that Lentz teaches the separation of blood into a plasma component and a cellular component. While Lentz acknowledges that it is possible to separate plasma from the blood, it is submitted that Le tz also *discourages* such a separation of blood (see col. 1, lines 51-62) on the basis that such a sepa ation "has a serious impact on the platelet level in the blood," "could not be considered for widespread use," and is "not very attractive for clinical use." Therefore, the Lentz reference, at best, is h ghly ambiguous on this point.

Second, a separation of cellular and acellular components offers no benefit if used in the method of Lentz. Lentz teaches a method of treating whole blood by passing the blood through a filter that separates factors in the blood based on size. Therefore, there is no advantage to be obtained by first separating the blood into cellular and acellular components, and then passing the components over the filter. Indeed, such a separation would be an added and unnecessary step in the method of Lentz. As such, the use of Lentz by the Examiner as a teaching of an element of the plasma separation in the stated rejection under 35 U.S.C. § 103 is not appropriate because the teachings of Lentz are, at most, ambiguous, and further, because no advantage in the Lentz process is obtained by separating cellular and acellular components of whole blood. Therefore, Lentz does not provide any ***motivation*** to combine the ambiguous discussion in Lentz with the other cited references in the manner suggested by the Examiner.

In contrast to Lentz, and in further support of the non-obviousness of the method claimed in the present application, there are *significant* advantages not recognized or suggested by the prior art to separating the acellular fraction from the cellular fraction prior to treatment of the bodily fluid. First, it is noted that the present method has the advantage over Lentz of selectively removing the targeted immune system inhibitor without affecting the action of desirable immune system stimulators and other blood components. This advantage is significantly enhanced by treating only the acellular portion of the blood. Specifically, certain of the molecules targeted for removal by the method of the present invention are soluble components which typically bind to an immune system stimulator. These soluble components often are homologues of *another* binding partner for the immune system stimulator, such that the interaction between the immune system stimulator and the other binding partner is inhibited by the binding of the soluble component to the immune system stimulator. Since the other binding partner is frequently a cell-associated binding partner (i.e., is present on cell surfaces), it is desirable, and indeed, may be highly advantageous, to bind the soluble immune system inhibitor *without binding the homologous cell-associated binding partner*. For example, sTNFRI is a soluble receptor for TNFα and TNFβ, which is produced through a proteolytic cleavage of the membrane receptor (mTNFRI) for TNFα and β. This proteolysis releases the extracellular domain of the mTNFRI from the cell surface and allows it to diffuse freely into the extracellular space. The sTNFRI, thus produced, retains fully the ability to bind TNF α and β with high affinity. Binding of TNFα and β by the sTNFRI prevents TNFα and β from binding to the

mTNFRI. Consequently, the pro-inflammatory and apoptotic effects normally induced through the crosslinking of mTNFRI by TNFα and β also are inhibited. Due to the significant structural similarity between sTNFRI and mTNFRI, contact of whole blood with a binding partner reactive with sTNFRI would permit binding to both the sTNFRI in circulation *and* the mTNFRI present on cell surfaces. This would have dire consequences for the patient, and would contradict the goals of the present method for several reasons. First, binding of the binding partner to mTNFRI would block its engagement by TNFα and β, thus, effectively reducing TNF-induced immune responses. Second, binding of an immobilized binding partner to mTNFRI would effect the depletion of mTNFRI-bearing leukocytes from whole blood, thereby diminishing immune competence. Third, and most undesirable, binding of an immobilized binding partner to mTNFRI would crosslink the receptor and act, therefore, as an agonist of TNFα and β. This would produce very significant and potentially fatal toxicities similar to those observed in human clinical trials of infusional TNFα.

By separating the whole blood into acellular and cellular components in the claimed method, these issues are avoided and the advantages of selectively removing the targeted immune system inhibitor while *maintaining* the action of desirable immune stimulators and other blood components is achieved. Since Lentz does not teach or suggest any selective removal of any specific factor, these advantages can not be realized by the method of Lentz.

Discussion of Selinsky

The Examiner contends that the reference of Selinsky et al. teach that the soluble TNFRI is removed by Ultraphoresis [sic], and that with the knowledge of Lentz, one would know that soluble immune system inhibitors can be removed from whole blood. The Examiner has also pointed to the statement in Selinsky et al.: "[w]e, therefore, propose the development of methods and/or reagents capable of specifically removing sTNFRI, or antagonizing its effects *in situ*, as unconventional, yet promising, strategies for cancer immunotherapy."

It is submitted that, although the statement in Selinsky et al. may cause one of skill in the art to consider how to antagonize or remove sTNFRI *in situ*, such a statement is merely an invitation to experimentation and opens the door for one of skill in the art to consider a wide range of possible approaches. Indeed, Selinsky et al. provide absolutely no guidance as to how one of skill in the art would go about such a task, but rather generally state that the "therapeutic utility of manipulating

sTNFRI levels *in vivo* has been demonstrated" and that "sTNFRI effectively inhibits immune responses *in vivo* and...its modulation is a legitimate therapeutic avenue." It is submitted that one of skill in the art, when presented with an invitation to manipulate the effects of a soluble protein, would look to a variety of conventional approaches to remove or manipulate the effects of that soluble protein *in vivo*, because such approaches are the most clinically desirable means of treating a patient. Conventional therapeutic manipulation of the immune system typically involves the administration of an antibody, peptide, protein, or small molecule that is designed to have a particular action in the patient. In fact, significant research has been directed to systems that enable the delivery of such reagents, including liposomes, targeting antibodies, combinations of liposomes and antibodies, small particles, emulsions, and other vehicles.

One conventional approach to modulating an immune response *in vivo* is to introduce into the subject a reagent that achieves the goal of selectively antagonizing or removing a target molecule once it is administered to a subject. For example, one method for removing or blocking the action of a soluble protein *in vivo* is to administer an antibody that binds to and effectively neutralizes the action of the target protein. Alternatively, a peptide or other soluble binding partner that competes with the target protein for binding to the natural ligand can be administered. As yet another alternative, a small molecule could be designed that targets and neutralizes the action of the target protein. Drug design for such *in vivo* applications is a common therapeutic approach when a target such as a soluble protein is available.

In contrast, to turn to an *ex vivo* approach such as that claimed in the present application is not conventional, and indeed, would be much less likely to be considered because it would conventionally be considered to be less direct, more expensive, and more invasive than the *in vivo* approaches discussed above. Such a method requires far greater manipulation of the patient and of the critical bodily fluids of the patient than an *in vivo* approach. Therefore, to arrive at the claimed *ex vivo* method would not have been an obvious extension of the statements made in Selinsky et al. that are referenced above.

4. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

2/20/01
Date

Mark D. Howell

2/20/01
Date

Cheryl L. Selinsky